KISSPEPTIN: A KEY COMPONENT OF THE REPRODUCTIVE SYSTEM

By: Brandon Dimick (PhD Student)

Dr. Shannon Stephens is a post-doctoral fellow in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Diego. She is a member of Dr. Alexander Kauffman’s lab, whose lab focuses on the regulation of reproduction. The overall goal of the laboratory is to understand how specific hormones and neurons interact to regulate the reproductive activity of mammals. An understanding of these mechanisms can allow for the possibility to treat infertility, create new contraceptive methods, and generate cures for other reproductive disorders that pertain to pubescence.

Dr. Stephens was invited by the Duquesne University Department of Biological Sciences to present a talk at their weekly seminar series. After getting to meet with Dr. Stephens during lunch, I was eager to learn more about her research. As a scientist, I have always been fascinated by the complex mechanisms in which specific molecules interact to regulate important biological systems. Reproduction is a perfect example of this concept, and I kept that in mind as I took my seat in the lecture hall.

Dr. Stephens began by summarizing the mechanisms of reproductive control in the mammalian brain. This involved a summary of the hypothalamic-pituitary-gonadal axis (HPG). In the brain, there is a specific class of neurons known as GnRH neurons. These neurons secrete GnRH, which stimulates cells in the pituitary gland that release
hormones such as LH and FSH. These hormones are responsible for inducing secretion in gonadal cells, thereby releasing hormones such as testosterone, estrogens, and progesterone. In a series of positive or negative feedback loops, the HPG is either induced or suppressed to regulate reproductive cycles and processes. This raises a question: what neurons upstream of the HPG interact with the sex hormones released by gonadal cells to generate the feedback loops that regulate the pathway? The answer was the focal point of Dr. Stephens talk.

Kisspeptin, the protein product of the kiss1 gene, appears to be vital for HPG regulation. Upstream of GnRH neurons are kisspeptin neurons. Populations of cells that secrete kisspeptin can be found in the brain at the anteroventral periventricular nucleus (AVPV) and the medial amygdala (MeA). Cells in the AVPV in particular are regulated by sex hormones such as estradiol and progesterone. Interestingly, it appears that the induction of kiss1 expression by progesterone is vital for the LH surge that ultimately leads to ovulation in female mammals. This was experimentally shown after progesterone receptors were knocked out in kisspeptin neurons. Female mice that had the knock-out mutation had a decreased number of litters as well as a decrease in the number of pups per litter. These knockouts, and similar experiments, showed a reduction in LH present during surges, as well as a reduction in frequency of surges. Therefore, it is evident that kiss1 activation by progesterone is vital for optimal ovulation, supporting the hypothesis that kisspeptin neurons are indeed the upstream regulatory component of the HPG.

Dr. Stephens went on to talk about how stress can affect kisspeptin expression and the LH surge. Previously, it has been shown that stress can affect reproduction by reducing ovulation. Dr. Stephens was interested to see if kisspeptin neurons were involved in this phenomenon as she has shown that kisspeptin is vital for the LH surge that induces ovulation. One way to analyze the effect of stress on an
organism is to look at corticosterone (CORT) levels. It was revealed that an increase in CORT leads to a decrease in the LH surge. This is because CORT lowers the expression of kiss1 in AVPV kisspeptin neurons.\textsuperscript{1} Stress may be affecting reproduction by inhibiting kisspeptin expression through CORT.

As mentioned previously, kisspeptin neurons are not only found in the AVPV; they are also in the MeA. The MeA is necessary for reproduction, social behavior, stress, and other processes in mammals. MeA kisspeptin neurons appear to be regulated by sex steroids. They are also regulated by GABA, the chief inhibitory neurotransmitter of mammals. However, GABA inhibition only occurs in MeA kisspeptin neurons and not in AVPV neurons.\textsuperscript{2} Dr. Stephens is interested to see how kisspeptin neurons affect MeA function. She is also interested to see what the protein products are that MeA kisspeptin neurons regulate, where the neurons project, and how they may affect mammalian reproduction.

The regulation of mammalian reproduction is complex and fascinating. It is also hard to imagine that the brain is ultimately responsible for the regulation of the reproductive system. Dr. Stephens hopes to unravel aspects of this complex web of interactions to lead to a better understanding of the systems that allow for mammals, such as us, to reproduce. Kisspeptin appears to be a vital component of the regulatory network. In the future, work can go on to decipher how kisspeptin in cells both in and outside of the AVPV can regulate reproduction and other systems. This can lead to better treatment options for those that suffer from infertility and other reproductive disorders.
References: